

CLAIMS

1. A method for the treatment of atherosclerosis in a patient in need of such treatment which comprises administering an effective amount of a bisphosphonate to the patient.
2. Use of a bisphosphonate in the preparation of a medicament for the treatment of atherosclerosis.
3. Use of a bisphosphonate to treat atherosclerosis associated with diseases or pathological conditions in mammals.
4. Use of a bisphosphonate to treat calcification associated with renal failure.
5. A method for the prevention and treatment of atherosclerotic calcification of blood vessels and valves in a patient, which comprises administering an effective amount of a bisphosphonate to the patient; or
use of a bisphosphonate in the preparation of a medicament for the prevention and treatment of atherosclerotic calcification of blood vessels and valves; or
use of a bisphosphonate in the preparation of a medicament for the prevention and treatment of calcification of blood vessels and valves associated with renal failure.
6. A method for the stabilisation of atherosclerotic plaques in a patient, which comprises administering an effective amount of a bisphosphonate to the patient; or
use of a bisphosphonate in the preparation of a medicament for stabilisation of atherosclerotic plaques.
7. A method for preventing or treating smooth muscle cell proliferation and migration in hollow tubes, or increased cell proliferation or decreased apoptosis or increased matrix deposition in a mammal in need thereof, comprising administration of a therapeutically effective amount of a bisphosphonate, e.g. zoledronic acid or a pharmaceutically acceptable salt thereof, optionally in conjunction with one or more other active ingredients.
8. A method for the treatment of intimal thickening in vessel walls comprising administration of a therapeutically effective amount of a bisphosphonate, e.g. zoledronic acid, or a pharmaceutically acceptable salt thereof, optionally in conjunction with one or more other active ingredients

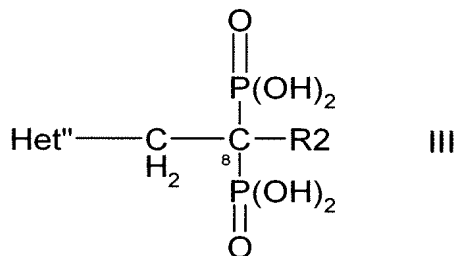
9. A method or use according to anyone of the preceding claims in which the bisphosphate is administered locally
10. A method or use according to claim 9 for the treatment of intimal thickening in vessel walls or stabilisation of vulnerable atherosclerotic plaques comprising the controlled delivery from a catheter-based device, intraluminal medical device or device applied to the external/adventitial aspect of the vessel of a therapeutically effective amount of a bisphosphonate, e.g. zoledronic acid, or a pharmaceutically acceptable salt thereof, optionally in conjunction with one or more other active ingredients
11. A method or use according to claim 9 wherein the bisphosphonate, e.g. zoledronic acid, or a pharmaceutically acceptable salt thereof is administered or delivered in conjunction with one or more other active ingredients selected from a calcineurin inhibitor, an EDG-Receptor agonist, an anti-inflammatory agent, a mTOR inhibitor agent, an antiproliferative agent, a microtubule stabilizing or destabilizing agent, a tyrosine kinase inhibitor, a compound which inhibits osteoclast activity, a compound which inhibits the PDGF receptor tyrosine kinase or a compound or antibody or antibody which binds to PDGF or reduces expression of the PDGF receptor, a compound or antibody which inhibits the EGF receptor tyrosine kinase or a compound which binds to EGF or reduces expression of the EGF receptor, a compound or antibody which inhibits the VEGF receptor tyrosine kinase or a VEGF receptor or a compound or antibody which binds to VEGF, a modulator of kinases.
12. A drug delivery device or system comprising a) a medical device adapted for local application or administration in hollow tubes and b) a therapeutic dosage of zoledronic acid or a pharmaceutically acceptable salt thereof being releasably affixed to the medical device.
13. A device according to claim 12 comprising b) a therapeutic dosage of a bisphosphonate, e.g. zoledronic acid or a pharmaceutically acceptable salt thereof in conjunction with a therapeutic dosage of one or more other active ingredients, each being releasably affixed to the medical device and the other active ingredient being selected from a calcineurin inhibitor, an EDG-Receptor agonist, an anti-inflammatory agent, a mTOR inhibitor agent, an antiproliferative agent, a microtubule stabilizing or destabilizing agent, a tyrosine kinase inhibitor, a compound which inhibits osteoclast activity, a compound or antibody which inhibits the PDGF receptor tyrosine kinase or a compound which binds to PDGF or reduces expression of the PDGF receptor, a compound or antibody which inhibits the

EGF receptor tyrosine kinase or a compound which binds to EGF or reduces expression of the EGF receptor, a compound or antibody which inhibits the VEGF receptor tyrosine kinase or a VEGF receptor or a compound which binds to VEGF, an inhibitor of a modulator of kinases.

14. A device according to claim 12 comprising b) a therapeutic dosage of a bisphosphonate, e.g. zoledronic acid, or a pharmaceutically acceptable salt thereof in conjunction with a therapeutic dosage of one or more other active ingredients, each being releasably affixed to the medical device and the other active ingredient being selected from a calcineurin inhibitor, a mTOR inhibitor agent, an EDG-Receptor agonist, an anti-inflammatory agent, a microtubule stabilizing or destabilizing agent, a compound which inhibits osteoclast activity, a compound or antibody which inhibits the PDGF receptor tyrosine kinase or a compound which binds to PDGF or reduces expression of the PDGF receptor, a compound or antibody which inhibits the EGF receptor tyrosine kinase or a compound which binds to EGF or reduces expression of the EGF receptor, a compound or antibody which inhibits the VEGF receptor tyrosine kinase or a VEGF receptor or a compound which binds to VEGF, an inhibitor of a modulator (i.e. antagonists or agonists) of kinases.
15. A method use or device according to anyone of claims 9-14 wherein the administration or delivery is made using a catheter delivery system, a device applied to the external/adventitial aspect of the vessel a local injection device, an indwelling device, a stent, a coated stent, a sleeve, a stent-graft, polymeric endoluminal paving or a controlled release matrix.
16. A method use or device according to any one of the preceding claims, in which the bisphosphonate is selected from the following compounds or a pharmaceutically acceptable salt thereof, or any hydrate thereof: 3-amino-1-hydroxypropane-1,1-diphosphonic acid (pamidronic acid), e.g. pamidronate (APD); 3-(N,N-dimethylamino)-1-hydroxypropane-1,1-diphosphonic acid, e.g. dimethyl-APD; 4-amino-1-hydroxybutane-1,1-diphosphonic acid (alendronic acid), e.g. alendronate; 1-hydroxy-ethidene-bisphosphonic acid, e.g. etidronate; 1-hydroxy-3-(methylpentylamino)-propylidene-bisphosphonic acid, ibandronic acid, e.g. ibandronate; 6-amino-1-hydroxyhexane-1,1-diphosphonic acid, e.g. amino-hexyl-BP; 3-(N-methyl-N-n-pentylamino)-1-hydroxypropane-1,1-diphosphonic acid, e.g. methyl-pentyl-APD (= BM 21.0955); 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid; 1-hydroxy-2-(3-pyridyl)ethane-1,1-diphosphonic acid (risedronic acid), e.g. risedronate, including N-methyl pyridinium salts thereof, for example N-methyl pyridinium iodides such as NE-10244 or NE-10446; 1-(4-chlorophenylthio)methane-1,1-diphosphonic acid (tiludronic acid), e.g. tiludronate; 3-[N-

(2-phenylthioethyl)-N-methylamino]-1-hydroxypropane-1,1-diphosphonic acid; 1-hydroxy-3-(pyrrolidin-1-yl)propane-1,1-diphosphonic acid, e.g. EB 1053 (Leo); 1-(N-phenyl-aminothiocarbonyl)methane-1,1-diphosphonic acid, e.g. FR 78844 (Fujisawa); 5-benzoyl-3,4-dihydro-2H-pyrazole-3,3-diphosphonic acid tetraethyl ester, e.g. U-81581 (Upjohn); 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethane-1,1-diphosphonic acid, e.g. YM 529; and 1,1-dichloromethane-1,1-diphosphonic acid (clodronic acid), e.g. clodronate.

17. A method use or device according to any one of claims 1-15, in which the bisphosphonate is a compound of Formula III



wherein

Het'' is an imidazolyl, 2H-1,2,3-, 1H-1,2,4- or 4H-1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl or thiadiazolyl radical which is unsubstituted or C-mono- or di-substituted by lower alkyl, by lower alkoxy, by phenyl which may in turn be mono- or disubstituted by lower alkyl, lower alkoxy and/or halogen, by hydroxy, by di-lower alkylamino, by lower alkylthio and/or by halogen and is N-substituted at a substitutable N-atom by lower alkyl or by phenyl-lower alkyl which may in turn be mono- or di-substituted in the phenyl moiety by lower alkyl, lower alkoxy and/or halogen, and R₂ is hydrogen, hydroxy, amino, lower alkylthio or halogen, lower radicals having up to and including 7 C-atoms, or a pharmacologically acceptable salt thereof.

18. A method use or device according to claim 17, in which the bisphosphonate is zoledronic acid, or a pharmaceutically acceptable salt thereof, or any hydrate thereof.